Immunogenicity of recombinant hepatitis B vaccine (rHBV) in recipients of unrelated or related allogeneic hematopoietic cell (HC) transplants


Current European and US guidelines for recombinant hepatitis B vaccine (rHBV) after hematopoietic-cell transplantation (HCT) vary. The European Group for Blood and Marrow Transplantation (EBMT) recommends rHBV starting 6 to 12 months after HCT. Immunization is optional in the Centers for Disease Control and Prevention (CDC) guidelines. Nevertheless, rHBV is required for re-entry to school and certain workplaces. To determine the immunogenicity of rHBV following HCT, the prevaccine and postvaccine titers of 292 allogeneic transplant recipients who were immunized with rHBV were analyzed. Immunization was initiated in patients off immunosuppression who achieved specific minimal milestones of immune competence. Overall, 64% of patients seroconverted. In multivariate analyses, response was adversely affected by age older than 18 years (P < .01) and history of prior chronic graft-versus-host disease (GVHD; P < .001) but not by donor type or by use of T-cell depletion, adoptive immunotherapy, or rituximab. By comparison, 89% of rHBV nonresponders mounted a 3-fold or greater rise in polio titers following 3 doses of inactivated poliovirus. These data demonstrate that the rate of seroconversion following rHBV is lower in allogeneic HC transplant recipients compared with age-matched healthy controls. The data emphasize the need to document prevaccine and postvaccine titers to ensure response and suggest that immunization guidelines based on time interval from HCT, irrespective of immune competence, may not ensure adequate protection against certain vaccine-preventable diseases. (Blood. 2006;108:2470-2475)

Introduction

Liver disease secondary to hepatitis B (HepB) virus is a vaccine-preventable disease. It is currently estimated that 1 million to 1.3 million individuals living in the United States are chronically infected with HepB virus, 5000 of whom will die each year from liver failure or hepatocellular carcinoma. In 1991, the Immunization Practices Advisory Committee (ACIP) recommended that all infants be vaccinated with recombinant hepatitis B vaccine (rHBV) starting at birth. In 1999, this recommendation was expanded to include all children younger than 18 years of age. Immunization of infants, children, and young adults with 3 age-appropriate doses of rHBV is associated with a greater than 95% seroconversion rate. Approximately 85% of healthy adults older than 40 years of age will develop positive titers following rHBV. The vaccine is less immunogenic in patients undergoing dialysis for end-stage renal disease, in patients with advanced liver disease due to hepatitis C, and in individuals immunocompromised by HIV (reviewed in Yu et al).

To date, a limited number of studies have evaluated the ability of HC transplant recipients to develop and maintain anti-HepB surface antigen (anti-HBs) titers following rHBV. In 1997, Li Volti et al evaluated anti-HBs titers in 20 hepatitis B virus–seropositive patients with thalassemia who underwent an unmodified allogeneic transplantation from an HLA-matched hepatitis B virus–seronegative sibling. Fifty percent of patients, including 9 who were previously immunized, became seronegative after HCT. Following 2 doses of the recombinant hepatitis B virus vaccine (Engerix-B), all patients developed a rise in anti-HBs. Machado11 and Machado et al12 reported a 100% seroconversion rate in 5 autologous and 45 HLA-matched related HC transplant recipients immunized at least 1 year after transplantation. Despite the excellent initial response, 60% of patients failed to sustain titers for more than 1 year following vaccination.11,12

To determine the ability of allogeneic transplant recipients to respond to rHBV, the immunization records and prevaccine and postvaccine titers of 292 patients vaccinated against HepB virus after an unrelated or related HCT were analyzed and compared with responses attained following vaccination with inactivated poliovirus (IPV). The effects of transplant type, patient age, stem-cell and donor type, use of T-cell depletion, history of prior acute or chronic graft-versus-host disease (GVHD), and the use of donor leukocyte infusion (DLI) and/or humanized monoclonal anti-CD20 antibody (rituximab) on rates of seroconversion and duration of response were assessed.

Patients, materials, and methods

This study was approved by the Memorial Sloan-Kettering Institutional Review Board. The medical records of all hepatitis B surface antigen (HBsAg)–negative patients who received an allogeneic HCT from an unrelated or related donor were retrospectively reviewed.

From the Memorial Sloan-Kettering Cancer Center, New York, NY.


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HBsAg-negative donor at Memorial Sloan-Kettering Cancer Center (MSKCC) from January 1, 1992, through April 15, 2004, and survived disease-free for longer than 1 year were reviewed. Three hundred seven patients were identified who received 3 recombinant DNA hepatitis B immunizations. Criteria for vaccination with rHBV and IPV at this center included a circulating CD4-cell count of at least 200 cells/μL, IgG level of 5 g/L (500 mg/dL) or greater at least 8 weeks following the last dose of intravenous immune globulin, and in vitro T-cell response to phytohemagglutinin at least 75% of the lower limit of normal. Patients with a prior history of GVHD (grade II-IV acute, limited, or extensive chronic GVHD) were eligible for revaccination if they were off systemic immunosuppressive therapy and had minimal or no signs or symptoms attributable to GVHD.14,15 Patients who were hepatitis C antibody positive but did not have severe liver disease at the time of vaccination were included in the analysis (n = 7). Patients were vaccinated with an age-appropriate dose of rHBV from either Merck (Whitehouse Station, NJ) or SmithKline Beecham Pharmaceuticals (Philadelphia, PA), as recommended by the manufacturers. The majority of patients were vaccinated at times 0, 1, and 6 months. Seventy-six percent of patients were vaccinated at MSKCC. All patients were evaluated at MSKCC before and after vaccination, including assessment of acute and chronic GVHD using established criteria.14

Titers against hepatitis B surface antigen (anti-HBs) were obtained prior to vaccination and 2 to 12 months following vaccination (median 5.9 months). Anti-HBs titers were measured using the AUSAB enzyme-linked immunosorbassay kit manufactured by Abbott Laboratories (Abbott Park, IL) using controls provided by the manufacturer. Patients who tested seronegative prior to vaccination were considered responders if their postvaccine serum testing showed absorbance above or equal to the kit cutoff value.

Fifteen (4.9%) of 307 vaccinated patients lacked follow-up titers and were excluded from analysis. The remaining 292 patients formed the basis of this report.

### Patient and transplant characteristics

Patient and transplant demographics are shown in Table 1. The median patient age at transplantation was 24 years, with a range of 0.2 to 69.0 years. The stem-cell donor was an HLA-A, -B, -DRB1–identical sibling; an HLA-mismatched family member; or unrelated donor in 65%, 9%, and 25% of cases, respectively. Sixty-five percent of patients received a T-cell–depleted HC transplant. Bone marrow was T-cell depleted by soybean lectin agglutination followed by rosetting with sheep red blood cells (n = 149) or treatment with the monoclonal antibody T10B9 and complement (n = 6) as previously described.17 G-CSF–mobilized peripheral-blood stem cells underwent positive selection for CD34+ stem cells followed by T-cell depletion by rosetting with sheep erythrocytes (n = 37). The only patients who received GVHD prophylaxis following a TCD HCT were the 6 recipients of an unrelated T10B9-treated bone marrow (BM) transplant.

The majority of recipients of a T-cell replete (unmodified) HC transplant (n = 100) received cyclosporine A (CyA) and methotrexate (n = 57) for GVHD prophylaxis. Two infants with severe combined immunodeficiency disease and one adult recipient of a syngeneic transplant did not receive GVHD prophylaxis after an HL-A-matched related unmodified transplantation. The remaining 40 patients received CyA (n = 6) or methotrexate alone (n = 3), CyA/steroids (n = 3), CyA/methotrexate/steroids (n = 7), CyA/alemtuzumab (n = 8), CyA/mycophenolic acid (n = 3), or tacrolimus and methotrexate (n = 10).

Twenty-five (8.6%) of the 292 patients received the monoclonal antibody rituximab for the treatment of a posttransplantation Epstein-Barr virus lymphoproliferative disorder (EBV-LPD; n = 8), EBV viremia (n = 12), autoimmune cytopenia (n = 2), or recurrent lymphoma (n = 3). Sixty-five patients received adoptive immunotherapy in the form of unfractionated donor lymphocytes for the treatment or prevention of an EBV-LPD (n = 13); to prevent or treat recurrent malignancy (n = 43), an autoimmune cytopenia (n = 1), or mixed T-cell chimerism (n = 4); or to promote immune reconstitution (n = 4).

### Statistical analysis

Frequency distributions of characteristics of patients who responded to rHBV or IPV vaccination and of the study cohort were summarized. Univariate and multivariate logistic regression analysis was used to examine the odds ratio for differences between vaccine responders and nonresponders. The Cuzick18 test for nonparametric trends across ordered groups was used to determine the effect of age categories on seroconversion rates. All statistical tests were considered significant at a 2-sided α-level of 0.05. Statistical analyses were performed using Stata 7 (release 7, 2000; Statcorp, College Station, TX).

### Results

The median time to initiate vaccination against hepatitis B was 23.4 months (range, 5.3–101.6 months) after HCT. There was no significant difference in the time to vaccination in T-cell–depleted

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>HLA-matched related</th>
<th>Unrelated</th>
<th>HLA-mismatched related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
<td>292</td>
<td>191</td>
<td>74</td>
<td>27</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>38.4</td>
<td>36.9</td>
<td>47.1</td>
<td>33.3</td>
</tr>
<tr>
<td>Age, median, y (range)</td>
<td>24.0 (0.2-69.0)</td>
<td>31.5 (0.2-69.0)</td>
<td>17.3 (0.6-55.5)</td>
<td>6.0 (0.2-46.8)</td>
</tr>
<tr>
<td>No. of children per group (%)</td>
<td>116/291 (40.2)</td>
<td>56/190 (29.5)</td>
<td>38/74 (51.4)</td>
<td>22/27 (81.5)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>124</td>
<td>76</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>Chronic leukemia</td>
<td>72</td>
<td>57</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Aplastic anemia/MDS</td>
<td>41</td>
<td>23</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>NHL/HD</td>
<td>28</td>
<td>19</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobinopathy</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune deficiency</td>
<td>17</td>
<td>6</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td><strong>Stem-cell product (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmodified</td>
<td>102 (35.1)</td>
<td>71 (37.3)</td>
<td>24 (27.0)</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>88</td>
<td>64</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>PBSCs</td>
<td>13</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cord blood</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TCD</td>
<td>179 (55.7)</td>
<td>119 (65.7)</td>
<td>50 (47.6)</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>153</td>
<td>102</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>PBSCs</td>
<td>26</td>
<td>17</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>TBI-containing regimen, %</td>
<td>76.9</td>
<td>74.3</td>
<td>88</td>
<td>55.6</td>
</tr>
</tbody>
</table>

MDS indicates myelodysplastic syndrome; NHL/HD, non-Hodgkin lymphoma/Hodgkin disease; PBSCs, peripheral-blood stem cells; and TBI, total body irradiation.
versus T-cell–replete transplant recipients (23.5 months versus 22.5 months). In patients younger than or older than 18 years of age, the median time to vaccination was 20.0 and 24.5 months after HCT, respectively. This reflected in part the time to achieve immune milestones required for revaccination in children and adults following HCT.

Two hundred sixty-seven of 292 patients were evaluable for seroconversion. This included 58 of 83 patients who were anti-HBs positive before HCT but lacked detectable titers when re-evaluated at a median 22.9 months (range, 5.6-73.6 months) after transplantation. At the time of vaccination, none of the 30 anti-HBs–negative patients who received a transplant from an anti-HBs–positive donor had passively transferred antibody detected.

Overall, 171 (64%) of 267 patients seroconverted after vaccination (Table 2), including 72 (73%) of 99 children and 99 (59%) of 168 adults ($P = .02$). There were no significant differences in the proportion of responders on the basis of pretransplantation diagnosis, stem-cell source (bone marrow or peripheral blood), donor type, use of T-cell depletion, inclusion of total body irradiation in the conditioning regimen, or seropositive donor (Table 2). In univariate analysis, younger age at transplantation ($P < .001$) and at initial immunization was associated with significantly higher rates of seroconversion ($P < .05$). Prior acute grade II-IV GVHD ($P = .02$) or chronic GVHD ($P < .001$) was associated with poorer response. In multivariate analysis, younger age ($P = .001$) remained associated with vaccine response. Chronic GVHD ($P < .001$) remained associated with nonresponse.

The results of vaccination with rHBV contrast sharply with results of IPV vaccination. At the time of revaccination (median, 19.2; range, 4.6-113.3 months after HCT), only 46 patients lacked residual polio titers. Ninety-six percent of 219 patients developed a 3-fold or greater rise in titer against all 3 polio serotypes after receipt of 3 IPV vaccinations given at 2-month intervals, including 70 (89%) of the 79 non-rHBV responders. Only younger age at transplantation ($P = .01$) was associated with improved response to IPV vaccination (Table 3).

Although the number of patients is small, the poorest response to rHBV was observed in recipients of an HLA-mismatched related HC transplant, irrespective of prior GVHD or use of T-cell depletion. Following an HLA-mismatched related HCT, 56% of

### Table 2. Characteristics of rHBV responders and nonresponders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responder, $n = 171$</th>
<th>Nonresponder, $n = 96$</th>
<th>Odds ratio*</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>22.0 (0.2-58.6)</td>
<td>33.8 (0.2-69)</td>
<td>0.97</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age younger than 18 years, no. (%)</td>
<td>72 (42.1)</td>
<td>27 (28.1)</td>
<td>1.86</td>
<td>.02</td>
</tr>
<tr>
<td>Sex, male, no. (%)</td>
<td>102 (59.7)</td>
<td>65 (67.7)</td>
<td>.71</td>
<td>.19</td>
</tr>
<tr>
<td>Diagnosis, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>76 (44.4)</td>
<td>37 (38.5)</td>
<td>1.28</td>
<td>.35</td>
</tr>
<tr>
<td>CML</td>
<td>42 (24.6)</td>
<td>27 (28.1)</td>
<td>0.83</td>
<td>.52</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>11 (6.4)</td>
<td>2 (2.1)</td>
<td>3.23</td>
<td>.13</td>
</tr>
<tr>
<td>MDS</td>
<td>14 (8.2)</td>
<td>9 (9.4)</td>
<td>0.86</td>
<td>.74</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>12 (7.0)</td>
<td>13 (13.5)</td>
<td>0.48</td>
<td>.08</td>
</tr>
<tr>
<td>Hemoglobinopathy</td>
<td>6 (3.5)</td>
<td>2 (2.1)</td>
<td>1.70</td>
<td>.52</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>10 (5.9)</td>
<td>6 (6.3)</td>
<td>0.93</td>
<td>.89</td>
</tr>
<tr>
<td>Donor, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-matched related</td>
<td>111 (64.9)</td>
<td>63 (65.6)</td>
<td>0.96</td>
<td>.91</td>
</tr>
<tr>
<td>HLA-mismatched related</td>
<td>14 (8.2)</td>
<td>11 (11.5)</td>
<td>0.69</td>
<td>.38</td>
</tr>
<tr>
<td>Unrelated</td>
<td>46 (26.9)</td>
<td>22 (22.9)</td>
<td>1.23</td>
<td>.47</td>
</tr>
<tr>
<td>Graft type, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cBMT</td>
<td>50 (29.2)</td>
<td>27 (28.1)</td>
<td>1.05</td>
<td>.85</td>
</tr>
<tr>
<td>cPBSCST</td>
<td>5 (2.9)</td>
<td>8 (8.4)</td>
<td>0.33</td>
<td>.06</td>
</tr>
<tr>
<td>TCD-BM</td>
<td>95 (55.6)</td>
<td>49 (51.0)</td>
<td>1.20</td>
<td>.48</td>
</tr>
<tr>
<td>TCD-PB</td>
<td>20 (11.7)</td>
<td>12 (12.5)</td>
<td>0.93</td>
<td>.85</td>
</tr>
<tr>
<td>Cord blood</td>
<td>1 (0.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient pretransplantation anti-HBs, no. (%)</td>
<td>126 (73.7)</td>
<td>71 (73.9)</td>
<td>0.98</td>
<td>.96</td>
</tr>
<tr>
<td>Positive†</td>
<td>37 (21.6)</td>
<td>21 (21.9)</td>
<td>0.98</td>
<td>.96</td>
</tr>
<tr>
<td>Unknown anti-HBs, negative core Ab (%)</td>
<td>8 (4.7)</td>
<td>4 (4.2)</td>
<td>1.12</td>
<td>.84</td>
</tr>
<tr>
<td>Donor anti-HBs, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>84 (49.1)</td>
<td>51 (53.1)</td>
<td>0.85</td>
<td>.53</td>
</tr>
<tr>
<td>Positive†</td>
<td>25 (14.6)</td>
<td>15 (15.6)</td>
<td>0.92</td>
<td>.83</td>
</tr>
<tr>
<td>Unknown§</td>
<td>62 (36.3)</td>
<td>29 (31.3)</td>
<td>1.25</td>
<td>.41</td>
</tr>
<tr>
<td>TBI regimen, no. (%)</td>
<td>125 (73.5)</td>
<td>72 (75.0)</td>
<td>.93</td>
<td>.79</td>
</tr>
<tr>
<td>DLI, no. (%)</td>
<td>37 (21.6)</td>
<td>28 (29.2)</td>
<td>0.67</td>
<td>.17</td>
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<tr>
<td>Rituximab, no. (%)</td>
<td>12 (7.0)</td>
<td>11 (11.4)</td>
<td>0.58</td>
<td>.22</td>
</tr>
<tr>
<td>Grade II-IV acute GVHD, no. (%)</td>
<td>21 (12.3)</td>
<td>22 (22.9)</td>
<td>0.47</td>
<td>.03</td>
</tr>
<tr>
<td>Chronic GVHD, no. (%)</td>
<td>15 (8.8)</td>
<td>27 (28.1)</td>
<td>0.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median d to first vaccine (range)</td>
<td>703 (171-2765)</td>
<td>778 (181-3444)</td>
<td>0.99</td>
<td>.012</td>
</tr>
<tr>
<td>Median age at first vaccine, y (range)</td>
<td>24 (1.6-60.6)</td>
<td>36.1 (8.69-66.9)</td>
<td>.97</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are the simple logistic regression odds ratios of an association between each characteristic and being a responder.
†Five of 58 anti-HBs-positive recipients were HepB core antibody positive.
‡Four of 40 anti-HBs-positive donors were HepB core antibody positive.
§One of 91 donors (23 related, 68 unrelated) with unknown anti-HBs status was HepB core antibody positive.

CML indicates chronic myeloid leukemia; cBMT, competitive bone marrow transplantation; cPBSCST, competitive peripheral-blood stem-cell transplantation; —, not applicable; and Ab, antibody. Additional abbreviations are explained in Table 1.
Table 4. Effect of age and transplant type on seroconversion rates following rHBV

<table>
<thead>
<tr>
<th>Age</th>
<th>Overall seroconversion rate</th>
<th>HLA-mismatched related</th>
<th>HLA-matched related</th>
<th>Unrelated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10 y, n = 56</td>
<td>44/56 (78.5)</td>
<td>11/16 (68.7)</td>
<td>19/25 (76.0)</td>
<td>14/15 (93.3)</td>
</tr>
<tr>
<td>10-20 y, n = 54</td>
<td>35/54 (64.8)</td>
<td>2/5 (40)</td>
<td>18/26 (69.2)</td>
<td>15/23 (65.2)</td>
</tr>
<tr>
<td>20-40 y, n = 78</td>
<td>52/78 (66.6)</td>
<td>12/50 (60)</td>
<td>41/58 (70.6)</td>
<td>10/18 (55.5)</td>
</tr>
<tr>
<td>Older than 40 y, n = 79</td>
<td>40/79 (50.6)</td>
<td>2/2 (0)</td>
<td>33/65 (50.7)</td>
<td>7/12 (58.3)</td>
</tr>
<tr>
<td>All ages</td>
<td>171/267 (64.8)</td>
<td>14/25 (56)</td>
<td>111/174 (63.8)</td>
<td>46/68 (67.6)</td>
</tr>
</tbody>
</table>

P = .04 by test for trend.
the ability of HCT patients to respond to childhood vaccines is less well studied. Moreover, the immunogenicity of vaccinations in recipients of an HLA-unrelated HC transplant, HLA-mismatched related HC transplant, or T-cell–depleted HC transplant remains largely unknown (reviewed in Machado9).

Our data demonstrate that 64% of patients vaccinated against hepatitis B after HCT develop protective titers. The immunogenicity of the recombinant vaccine is decreased, however, in patients older than 18 years of age when compared with age-matched controls and in patients with a history of grade II-IV acute GVHD or chronic GVHD. In a smaller study of allogeneic or autologous HC transplant recipients, Machado et al12 also found an association of older age and prior chronic GVHD with poorer response to the rHBV. Similar to reports in healthy controls, approximately 50% of allogeneic transplant recipients who fail an initial series of rHBV will respond to a second series.1 In contrast to the results of rHBV, response to polio virus was excellent in all age groups and not adversely affected by prior acute or chronic GVHD. Ninety-six percent of patients responded to IPV vaccination. The greater response to IPV vaccination likely reflects in part the multiple antigenic peptides included in the Salk vaccine compared with the single small envelope (S protein) contained in recombinant hepatitis B vaccines currently licensed in the United States (reviewed in Poland and Jacobson3). It is also possible that responses reflect expansion of memory T and B cells persisting after childhood immunization, which were transferred in the unmodified or even the T-cell–depleted grafts.

The impact of age and prior chronic GVHD on hepatitis B responses observed in this study occurred despite our requirement that patients be off all immunosuppressive medications and that they achieved specific minimal milestones of T- and B-cell immune competence. Our rationale for this approach was based on concerns that vaccination prior to the development of these milestones would be less effective in inducing immediate and long-term T- and B-cell responses. Indeed, qualitative and quantitative differences in effector and memory helper T and/or B cells may differentiate long-term responders and nonresponders.19,20 Although all HC transplant recipients are subject to a varying period of T and B lymphocytopenia and subsequent functional incompetence despite return of normal numbers of T and B cells, the severity and duration of this immuno incompetence is not uniform across transplant types and/or patients of all ages.21,22 For these reasons, we hypothesized that immunization guidelines based on fixed times after HCT23,24 are unlikely to result in adequate protection against vaccine-preventable diseases in all patient groups. Indeed, based on studies from our own series and that of others,11,12 vaccination with rHBV starting at 6 or 12 months following HCT, particularly in older adults, will likely precede reconstitution of required memory and effector lymphoid populations necessary for long-term immunity.19,20 In the study of Machado et al12 60% of patients vaccinated lost protective anti-HBs titers by one year following immunization. In contrast, in our own study in which patients were immunized only after recovering a specific level of immune reconstitution (which varied in time from 6 months to >2 years), only 20% of patients lost protective levels of antibody by 5 years after immunization. Clearly, differences in several variables such as age, incidence and severity of acute and/or chronic GVHD, and/or the type of transplant might contribute to these differences. However, differences in the durability of the response do underscore the need for prospective studies to examine and compare the effectiveness of current vaccination protocols.

Studies in healthy individuals have demonstrated that at least 60% of children vaccinated as infants and 98% of young adults vaccinated in adolescence retain protective titers 10 years following HepB vaccination.25 The 1990 measles epidemic in the United States (reviewed in Ada26), the spread of measles in a bone marrow transplantation (BMT) unit in São Paolo,27 the outbreak of varicella in a daycare center28 in which the index case and the majority of affected children had previously received varicella virus vaccine live, and the recent increase in pertussis in healthy29 individuals and oncology patients30 underscore the importance of systematic evaluation of the duration of positive antibody titers following vaccination, even in immunocompetent individuals. Despite the retrospective nature of this study, it underscores the need to obtain prevaccine and postvaccine titers in order to ensure seroconversion and long-term immunity against hepatitis B virus and suggests that studies using higher doses of HBV in patients older than 40 years or with a prior history of GVHD, a strategy efficacious in dialysis patients, should be undertaken (reviewed in Poland and Jacobson3 and Yu et al4). Prospective trials that compare initiation of immunization based on the time interval from transplantation versus schedules based upon achievement of specific benchmarks of functional immune reconstitution, irrespective of the time elapsed from transplantation, are needed.

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References


Immunogenicity of recombinant hepatitis B vaccine (rHBV) in recipients of unrelated or related allogeneic hematopoietic cell (HC) transplants